DRUG NAME: Tamoxifen

SYNONYM(S): Tam, Tamoxifene

COMMON TRADE NAME(S): APO-TAMOX®, GEN-TAMOXIFEN®, NOLVADEX-D®, NOVO-TAMOXIFEN®, TAMOFEN®

CLASSIFICATION: endocrine anti-hormone

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Tamoxifen and several of its metabolites are thought to act as estrogen antagonists, by competitively binding to estrogen receptors on tumour and other tissue targets, producing a nuclear complex that decreases DNA synthesis.[1,2] This mechanism appears to have cytostatic effects, causing cells to accumulate in G0 and G1 phases.[1] Tamoxifen may also have cytotoxic activity; tamoxifen may induce apoptosis independent of estrogen receptor expression.[3,4] It is also recognized that tamoxifen acts as an estrogen agonist on endometrium, bone and lipids.[2]

PHARMACOKINETICS:

Interpatient variability	considerable variation in serum concentrations after single doses and at steady state;[5,6] genetic polymorphism may influence the efficacy and toxicity of tamoxifen and its metabolites[7-9]	
Oral Absorption	well absorbed[1]	
	time to peak plasma concentration	3-7h
Distribution	high concentrations found in uterus and breast tissue[1]	
	cross blood brain barrier?	yes[10]
	volume of distribution[11]	20 L/kg
	plasma protein binding[1]	99%
Metabolism	metabolized by hepatic cytochrome[1] P450; major CYP3A4, 2C8/9, 2D6; minor 2A6, 2B6, 2E1	
	active metabolite(s)	N-desmethyltamoxifen, 4-hydroxytamoxifen, and 4-hydroxy-N-desmethyltamoxifen (endoxifen)[7]
	inactive metabolite(s)	yes
Excretion	extensive enterohepatic circulation[2,5]	
	urine[1]	9-13%
	feces[1,2,5]	26-65%, excreted into bile[12]
	terminal half life	5-7 days, range 3-21 days; major metabolite 9-14 days[5]
	clearance	no information found

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
Brain tumours[13-15]
*Breast cancer[2,17,18]
Melanoma[1,21]
Soft tissue sarcoma[1,22]

Other uses:
Carcinoid tumour[5,16]
Endometrial cancer[16,19,20]
Pancreatic cancer[1]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Carcinogenicity: Tamoxifen is carcinogenic.[5]

Mutagenicity: Not mutagenic in Ames test and in the mammalian *in vivo* mutation test.[23] It is not known if tamoxifen is clastogenic.[24]

Fertility: Tamoxifen may cause disturbances of menstrual cycle, including infrequent or light menstruation and amenorrhea.[2] Tamoxifen does not induce menopause. Premenopausal women should be advised not to become pregnant while taking tamoxifen.[2] Tamoxifen has been used to treat infertility.[25-29] Tamoxifen has caused impotence in men.[30]

Pregnancy: FDA Pregnancy Category D.[1] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[31] Tamoxifen may inhibit lactation.[31]

Special populations: The risk of serious adverse events is higher in patients older than ***50 years of age***.[5] Women of ***childbearing potential*** should initiate tamoxifen during menstruation; barrier or nonhormonal contraceptives should be used and pregnancy avoided for 2 months after tamoxifen is discontinued.[1] ***Porphyric patients*** must avoid tamoxifen, as tamoxifen has been associated with acute attacks of porphyria.[7]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[32] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	hypersensitivity reactions (≤3%)[1,23,33]
	vasculitis[5,34]
blood/bone marrow/ febrile neutropenia	myelosuppression; anemia,[2,33] leukopenia,[33,35] neutropenia,[23] thrombocytopenia[23]; transient[5] (≤10%)[1,33,36,37]
cardiovascular (arrhythmia)	QT prolongation[38]
cardiovascular (general)	cardiovascular events (4%, severe 1%)[39]
	hypertension (7-11%)[36,37,40]
	ischemic heart disease (1-3%, severe 0.6%)[37,39,41]
	thromboembolic events (2-5%, severe 1-2%)[37,39-43]
constitutional symptoms	fatigue (4-24%, severe 2%)[1,40-42]
	sweating (6-18%, severe 3%)[36,42,43]
	weight gain (8-9%)[36,40]
	weight loss (23%)[1]
dermatology/skin	alopecia (<5%)[1,43]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	cutaneous lupus erythematosus[44]
	nail changes (3%)[37]
	porphyria cutanea tarda[45]; has occurred after years on treatment[45]
	radiation recall[46-48]
	rash (<13%)[1,23,36,40]
	skin changes (6-19%)[1]
	Stevens-Johnson syndrome, erythema multiforme, bullous pemphigoid (<1%)[1]
endocrine	***hot flashes (25-81%, severe 4%)[1,2,5,39,41,42]***
gastrointestinal	anorexia (1-3%)[1,43]
	constipation (1-8%)[1,36,40,43]
	diarrhea (2-7%, severe 0.04%)[36,37,40,42]
	dyspepsia (6%)[36]
	dry mouth (2%)[37]
	nausea (5-26%, severe 0.7%)[1,2,36,40-43]
	vomiting (2%)[43]
hemorrhage	hemorrhage[5]
	vaginal bleeding (2-23%, severe 0.1-0.3%)[1,36,39-42]
hepatobiliary/pancreas	cholestasis (≤0.1%)[33]
	gallstones; generally occurs after 2-3 years of treatment[49]
	pancreatitis (<1%)[1,5,33]
	liver dysfunction, hepatitis (<1%)[1,33,37]
infection	urinary tract infection (10%)[36,37]
	vulvovaginal candidiasis[50] (4%)[37]
lymphatics	peripheral edema (8-11%)[36,40]
metabolic/laboratory	elevated creatinine[5]
	hypercalcemia (<1%)[1]; with metastatic disease; generally occurs shortly after starting treatment[2,5]
	altered lipid profile; decreased total and LDL cholesterol, decreased HDL cholesterol,[5] hypercholestremia (3%)[37], increased triglycerides (≤1%)[5,33,51,52]; onset may be delayed months or years[5,51,52]
	elevated liver function tests[5,23] (≤1%)[33]
musculoskeletal	arthritis (14%)[36]
	arthrosis (4%)[40]
	favorable effect on bone mass[53-55]
	fractures (4-8%)[36,37,39,41]
	osteoporosis (6-7%)[36,37,42]
neurology	anxiety (6%)[36]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	depression (4-12%, severe 0.2%)[36,42]
	dizziness (8-12%, severe 0.6%)[36,42]
	ischemic cerebrovascular events (1-3%, severe 1%)[39-41]
	insomnia (6-17%, severe 1%)[36,40,42]
	paresthesia (5%)[36,37]
ocular/visual	***cataracts (<7%)***[1,23,33,36,40-42]
	corneal changes (≤0.1%)[33]
	retinopathy (≤1%)[1,23,33]; can occur within weeks-years[56]
	vision changes (6%, severe 0.4%)[42]
pain	abdominal pain (7-9%)[36]
	arthralgia/myalgia (4-29%, severe 0.4-0.9%)[39,41,42]
	back pain (10%)[36]
	bone pain (6%)[41]; generally occurs shortly after starting treatment[2,5]
	breast pain (6%)[36]
	chest pain (5%)[36]
	cramps (4%, severe 0.2%)[42]
	headache (2-16, severe 0.8%)[36,40,42,43]
	pain not specified (16%)[36]
	tumour pain; generally occurs shortly after starting treatment[2]
pulmonary	cough (4-10%)[1,5,36,40]
	pharyngitis (≤14%)[36,40]
	pneumonitis (<1%)[1]
renal/genitourinary	endometrial polyps, hyperplasia, endometriosis (≤1%)[1,33]
	ovarian cysts (<3%)[1,5,33,57,58]
	pruritus vulvae (<1%)[1], vulvovaginitis (5%)[36]
	urinary incontinence (4%)[37]
	uterine fibroids (≤1%)[1,23,33]
	non-infectious vaginal discharge, leukorrhea (9-13%)[36,41,42]
	vaginal dryness (<3%)[1,40]
secondary malignancy	***endometrial cancer (0.8%)***[37,41]***; uterine sarcoma***
sexual/reproductive function	impotence (<1%)[1]
	menstrual dysfunction
	priapism[5]
syndromes	flu syndrome (6%)[36]
	tumour flare (<10%)[33]***; generally occurs shortly after starting treatment***[2]

Adapted from standard reference[2] unless specified otherwise.

Hot flashes are one of the most common adverse events reported in women taking tamoxifen, but are rarely severe.[5] If severe, they may be controlled in some patients by a decreased or divided dose. Patients who have their sleep interrupted by drenching night sweats may benefit by taking their tamoxifen in the morning.[32] Several medications have been shown to decrease the frequency and severity of hot flashes (See BC Cancer Agency Breast Tumour Group/Cancer Management Guidelines/Breast/Follow-up/Post-menopausal Replacement Therapy).[59,60] Occasionally tamoxifen must be discontinued due to severe hot flashes which significantly decrease quality of life.[32]

Tamoxifen flare response: A transient increase in bone pain, local disease flare (increase in size of preexisting lesions, swelling and redness) and/or hypercalcemia may occur at the initiation of therapy in patients with metastatic disease.[2] Serum calcium should be evaluated in any patient with extensive bony metastases on tamoxifen who have symptoms suggestive of hypercalcemia.[32] The so-called tamoxifen flare response may be a favourable sign,[2] although hypercalcemia may require treatment.

Endometrial changes: Tamoxifen has a stimulant effect on the endometrium, possibly by acting as a partial estrogenic agonist.[5] Tamoxifen use has been associated with an increased incidence of endometrial changes, including hyperplasia, polyps, uterine fibroids, and endometriosis.

Uterine malignancies associated with tamoxifen are typically adenocarcinomas of the endometrium; uterine sarcomas, an endometrial cancer with poor prognosis, have also been rarely reported.[5,61] The relative risk of endometrial cancer increases with duration of tamoxifen therapy; this relative risk is small, and must be weighed against the potential benefits of tamoxifen.[7] Women receiving or who have received tamoxifen should have routine gynecological care and should be advised to report any abnormal gynecologic symptoms, such as menstrual irregularities, abnormal vaginal bleeding or discharge, or pelvic pain and pressure immediately.[5] Imaging, including endovaginal ultrasound and/or endometrial biopsy may be necessary to rule out malignancy.[32]

Ocular changes (retinopathy, corneal opacities, decreased visual acuity) have been reported in patients receiving tamoxifen.[2,62] A modest increase in the risk of developing cataracts has been associated with tamoxifen treatment.[63,64] The relationship between tamoxifen dose and cataract formation is not known.[63] Cataract formation may be due to inhibition of chloride channels in the lens by tamoxifen.[65] Macular degeneration does not appear to predispose patients to tamoxifen-related ocular toxicity, nor does tamoxifen accelerate progression of macular degeneration.[62] Patients receiving or who have received tamoxifen should be questioned about symptoms of ocular toxicity during follow-up and should seek prompt medical attention for changes in vision.[5,62]

Thromboembolic events, including deep vein thrombosis, stroke, and pulmonary embolism are increased with tamoxifen.[2] Use tamoxifen with caution in individuals with a history of thromboembolic events,[1] particularly those not receiving systemic anticoagulation therapy.

Hepatotoxicity usually consists of transient asymptomatic elevation of hepatic enzymes.[2] However, more serious liver abnormalities, including fatty liver, cholestasis, and hepatitis, have occurred infrequently;[2] rarely fatalities have been reported.[56]

Lipid profile: Tamoxifen favorably affects lipid profiles by decreasing total and low-density lipoprotein cholesterol concentrations[5]; this effect does not translate to a reduced risk of ischemic heart disease.[5,64,66] Less favorably, tamoxifen appears to moderately decrease high-density lipoprotein cholesterol concentrations and increase triglyceride levels.[2,5] Rarely, cases of pancreatitis have occurred.[2] Periodic monitoring of plasma cholesterol and triglyceride concentrations is advised for patients taking tamoxifen who have preexisting hyperlipidemias or other clinical indications.[5,17,18]

Myelosuppression has been reported with tamoxifen.[2] Temporary decreases in platelet and leukocyte counts may occurr.[2] Hemorrhagic tendencies are uncommon, and platelet counts have returned to normal without treatment interruption.[2] If myelosuppression is suspected, monitor complete blood counts.[2,17,18] Use tamoxifen with caution in patients with thrombocytopenia or leukopenia.[2]

Bone mass: Tamoxifen generally has a favorable effect on bone mass. Tamoxifen reduces bone resorption and decreases bone turnover as manifested by reductions in bone turnover markers and increases in bone density.[5] Tamoxifen acts mainly on trabecular bone, such as lumbar spine, and has little effect on cortical bone.[5] The effect of tamoxifen on bone density may depend on menopausal status, as premenopausal women have demonstrated a loss of bone mineral density of the lumbar spine and hip.[5] Further information is needed to evaluate the long-term effects of tamoxifen on the risk of osteoporosis and fracture.[5]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aldesleukin[67]	increased risk of hypersensitivity reactions	unknown	monitor for signs and symptoms of hypersensitivity reactions
aminoglutethimide[68,69]	decreased tamoxifen and its active metabolites concentrations	increased metabolism of tamoxifen	avoid concurrent use
anastrozole	tamoxifen decreases plasma anastrozole level by 27%, but has no significant effect on estrogen suppression by anastrozole[70]; anastrozole has no significant effects on the pharmacokinetics of tamoxifen[70,71]		
bexarotene[72-74]	35% decrease in tamoxifen plasma concentrations	unknown; likely be due to induction of CYP 3A4 by bexarotene	clinical significance unclear; consider alternate agent(s)
bromocriptine[5]	increased tamoxifen concentrations	decreased metabolism of tamoxifen	caution
cyclophosphamide[75]	decreased cytotoxic effects of cyclophosphamide	unknown	avoid concurrent use; start adjuvant tamoxifen after chemotherapy is completed
cytotoxic agents[2]	increased risk of thromboembolic events	unknown	caution
doxorubicin[75]	decreased cytotoxic effects of doxorubicin	unknown	avoid concurrent use; start adjuvant tamoxifen after chemotherapy is completed
estrogens[56]	may interfere with therapeutic effect of tamoxifen	may counter the estrogen suppression effect of tamoxifen	*see below
exemestane[76]	no significant effects on tamoxifen or exemestane pharmacokinetics		
fluorouracil[75]	decreased cytotoxic effects of fluorouracil	unknown	avoid concurrent use; start adjuvant tamoxifen after chemotherapy is completed
grapefruit juice[77]	may affect bioavailability of tamoxifen and its active metabolites[78,79]	may inhibit CYP3A4 metabolism of tamoxifen in the intestinal wall	†see below

AGENT	EFFECT	MECHANISM	MANAGEMENT
letrozole	tamoxifen decreases plasma letrozole level by 38%, but has no significant effect on estrogen suppression by letrozole[80]; letrozole has no effects on the pharmacokinetics of tamoxifen and its major metabolites[81]		
mitomycin[69]	increased risk of hemolytic uremic syndrome	unknown	avoid concurrent use
paroxetine[9,82,83] and other selective serotonin inhibitors that inhibit cytochrome P450 2D6	reduced tamoxifen active metabolite concentrations	inhibits CYP2D6 metabolism of tamoxifen	‡see below
rifamycins (e.g., rifabutin, rifampin, rifapentine)[33,84-86]	reduced tamoxifen concentrations; potentially increased levels of NDM-TAM metabolite, and subsequently endoxifen (active metabolite)	induces CYP3A4 metabolism of tamoxifen	no alteration of efficacy expected; clinical impact is unknown
thyroid function tests[5,87,88]	elevated thyroid hormone levels (T_4 and T_3)	increased thyroxine-binding globulin	none, thyroid function does not appear to be affected
warfarin[2,84]	delayed, major, possible; increased anticoagulant effect	unknown	monitor prothrombin time, adjust warfarin dose accordingly

Tamoxifen, N-desmethyltamoxifen, and 4-hydroxytamoxifen are inhibitors of cytochrome P450 mixed function oxidases, (isoenzymes 2B6, 2C8/9 and 3A4).[1,5] The effect of tamoxifen on medications that require mixed function oxidases for activation is unknown.[5]

CYP3A4, CYP2D6 and, CYP 2C8/9 inhibitors may decrease metabolism and increase tamoxifen plasma concentrations.[1,30] Tamoxifen active metabolite concentrations may be affected.[85] The clinical impact of this interaction is not known.

CYP3A4, CYP2D6, and CYP 2C8/9 inducers may increase metabolism and decrease tamoxifen plasma concentrations.[1,30] Tamoxifen active metabolite concentrations may be affected.[85] The clinical impact of this interaction is not known.

Estrogen use with tamoxifen: While hormone replacement therapy is not recommended following estrogen receptor positive breast cancer or while on tamoxifen, postmenopausal symptoms can cause considerable distress to patients; replacement therapy may be considered if other treatment options fail.[59] If estrogen is used, prescribe the lowest dose to relieve symptoms, monitor patient carefully and consider short term use.[59] For vaginal complaints such as dyspareunia, dryness and sexual dysfunction, REPLENS®, a long-lasting vaginal moisturizer can be tried.[32] If ineffective, low dose topical estrogen may then be considered.[32,59] ESTRING® produces a local effect with systemic levels measurable only for the first 24 hours of the three month ring.[32] PREMARIN® cream can be used but may have variable systemic levels related to the absorption through the vaginal tissues. The potential risks and benefits should be discussed, the lowest dose to relieve symptoms should be used, and treatment should be assessed regularly.[59]

†***Grapefruit juice and tamoxifen:*** Grapefruit juice inhibits the CYP 3A4 metabolism of tamoxifen in the intestine and may increase tamoxifen plasma levels.[77] The clinical significance of a low rate of intestinal metabolism to active metabolites is unknown. Monitor for tamoxifen toxicity.

‡***Antidepressant use with tamoxifen:*** The metabolism of tamoxifen to active 4-hydroxy-N-desmethyl-tamoxifen (endoxifen) metabolites is inhibited by paroxetine, a potent inhibitor of CYP2D6.[83] Other Selective Serotonin Reuptake Inhibitors (SSRI's) that inhibit CYP2D6 also inhibit the metabolism of tamoxifen.[83] The magnitude of reduction in endoxifen plasma concentration associated with CYP 2D6 inhibitors also depends on variations in CYP

2D6 genotypes.[8,9,83] The minimally active levels of tamoxifen and its active metabolites are not known.[89] The clinical significance of a low rate of hydroxylation to endoxifen is not known; the potential benefit of antidepressant use must be weighed against the potential risk.[8,9,12,90] Antidepressants that are weak inhibitors or do not inhibit CYP 2D6 may be considered.[83] **(More information under "List of Antidepressants and Tamoxifen Interactions" – see document after References)**

SUPPLY AND STORAGE:

Tablets: Apotex, Genpharm, and Novopharm supply tamoxifen as 10 mg or 20 mg tablets.

AstraZeneca supplies tamoxifen as a 20 mg tablet. Selected non-medicinal ingredients: lactose.

Aventis Pharma supplies tamoxifen as 10 mg or 20 mg tablets. Selected non-medicinal ingredients: lactose.

Store tamoxifen at room temperature and protect from light.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

Oral:	***20 mg PO once daily***[5,17,18] ***20 mg (range 20-120 mg) PO twice daily***[5,13-15,21,22] dose greater than 20 mg should be administered in two divided doses
Concurrent chemotherapy:	tamoxifen should be started after completing chemotherapy in most circumstances[75]
Concurrent radiation:	tamoxifen may be started before commencing or after completing radiation treatment, initiating treatment during radiation therapy should be avoided[91]
Dosage in renal failure:	no adjustment required[11,92]
Dosage in hepatic failure:	adjustment required, no details found[93]; dosing may be based on serum levels of tamoxifen and its active metabolites[94]
Dosage in dialysis	no adjustment required[93]

Children:

safety and effectiveness not established in children[69]

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List of Antidepressants and Tamoxifen Interactions

(Developed by BCCA Provincial Drug Information Service, in collaboration with the Breast Tumour Group and Vancouver Cancer Centre psychiatrists – last updated 17 September 2014)

Tamoxifen is converted into its active metabolites 4-hydroxy-tamoxifen, endoxifen and other active metabolites by the CYP2D6 liver enzyme. The efficacy of tamoxifen may vary between individuals due to heterogeneous genetic variation in CYP2D6 activity, and by co-administration of a number of drugs that may modulate the activity of the enzyme.

Selective Serotonin Reuptake Inhibitors (SSRI's) are a commonly used class of anti depressants which inhibit CYP2D6 to varying degrees. Concurrent administration of some SSRIs and tamoxifen has been shown to lower levels of endoxifen, but not of 4-hydroxy-tamoxifen. The clinical implications of this decline in endoxifen levels are unclear because tamoxifen concentrations do not appear to change substantially. However, retrospective evidence presented at ASCO 2009 reported that concomitant use of tamoxifen and moderate/potent CYP2D6 inhibitors significantly increased the risk of breast cancer recurrence. In the SSRI subanalysis, moderate or potent, CYP2D6 inhibitors were associated with 25-92% greater relative risk of breast cancer recurrence, depending on duration of co-exposure, compared with taking no SSRIs with tamoxifen. Weak CYP2D6 inhibitors were not associated with an increased breast cancer recurrence in this study. A recent retrospective study from Ontario also suggests that the greater risk of breast cancer recurrence with paroxetine may be associated increased cancer death.

Drugs that could potentially cause reduction in efficacy and thus should be used with caution include any strong CYP2D6 inhibitors such as: fluoxetine, paroxetine, chlorpromazine, miconazole, quinine, and bupropion. Moderate inhibitors include: ketoconazole, trazodone and amiodarone. The safest course of action is to avoid co-administration of tamoxifen and any of these medications. However, each individual's particular need and circumstances should be evaluated to determine what is best for them.

Serotonin Norepinephrine Reuptake Inhibitors (SNRI's) like venlaflaxine and desvenlafaxine are weak CYP2D6 inhibitors and do not lower the concentration of endoxifen. These are better choices for women taking tamoxifen who also require medication for depression or relief of hot flashes.

The following table lists examples of commonly used antidepressants and their association with CYP2D6 and tamoxifen. NOTE: The following table is not an all-inclusive list and the contents are subject to change over time. Therefore, this table is not intended to be used as the sole source of information regarding antidepressant-tamoxifen interactions and should always be used in conjunction with standard drug interaction resources.

Class of drugs	*Drug*	*CYP2D6 activity*	*Tamoxifen Interaction*
SSRIs	Fluoxetine	Strong inhibitor	Probable
	Paroxetine	Strong inhibitor	Probable
	Sertraline	Moderate inhibitor	Possible
	Fluvoxamine	Weak inhibitor	Not likely
	Citalopram	Weak inhibitor	Not likely
	Escitalopram	Weak inhibitor	Not likely
SNRIs	Duloxetine	Moderate inhibitor	Possible
	Venlafaxine	Weak inhibitor	Not likely
	Desvenlafaxine	Weak inhibitor	Not likely
MAOIs	Tranylcypromine	Moderate inhibitor	Possible
	Selegiline	Weak inhibitor	Not likely
Tricyclics	Clomipramine	Moderate inhibitor	Possible
	Amitriptyline	Weak inhibitor	Not likely
	Desipramine	Moderate inhibitor	Possible
	Nortryptyline	Weak inhibitor	Not likely
	Imipramine	Moderate inhibitor	Possible
	Doxepin	Major substrate	Not likely
	Trimipramine	Major substrate	Not likely
Others	Buspirone	Minor substrate	Not likely
	Trazodone	Major substrate	Not likely
	Mirtazapine	Weak inhibitor	Not likely
	Bupropion	Strong inhibitor	Probable

Appendix:

Drug interactions assigned documentation levels as outlined by Facts & Comparisons 4.0:

- Certain: proven to occur in studies or recommended by reputable guidelines
- Probable: very likely, but not proven in controlled studies
- Possible: could occur, but data are very limited
- Not likely: no good evidence of an altered clinical effect

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